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# NOTICE OF ALLOWANCE AND FEE(S) DUE

76595 7590 07/27/2009

LANDO & ANASTASI, LLP
W2023
ONE MAIN STREET
SUITE 1100
CAMBRIDGE, MA 02142

| EXAMINER | |
|---|---|
| STEADMAN, DAVID J | |
| ART UNIT | PAPER NUMBER |
| 1656 | |

DATE MAILED: 07/27/2009

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/955,737 | 09/19/2001 | Rajiv Chopra | W2025-701110/AM100448 | 9455 |

TITLE OF INVENTION: METHOD FOR IDENTIFYING AGENTS THAT INTERACT WITH BETA-SITE APP CLEAVING ENZYME (BACE)

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | NO | $1510 | $300 | $0 | $1810 | 10/27/2009 |

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

**HOW TO REPLY TO THIS NOTICE:**

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

**IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.**



PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

# PART B - FEE(S) TRANSMITTAL

**Complete and send this form, together with applicable fee(s), to: Mail** **Mail Stop ISSUE FEE**
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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

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Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

| |
|---|
| (Depositor's name) |
| (Signature) |
| (Date) |

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/955,737 | 09/19/2001 | Rajiv Chopra | W2025-701110/AM100448 | 9455 |

TITLE OF INVENTION: METHOD FOR IDENTIFYING AGENTS THAT INTERACT WITH BETA-SITE APP CLEAVING ENZYME (BACE)

| APPLN. TYPE | SMALL ENTITY | ISSUE FEE DUE | PUBLICATION FEE DUE | PREV. PAID ISSUE FEE | TOTAL FEE(S) DUE | DATE DUE |
|---|---|---|---|---|---|---|
| nonprovisional | NO | $1510 | $300 | $0 | $1810 | 10/27/2009 |

| EXAMINER | ART UNIT | CLASS-SUBCLASS |
|---|---|---|
| STEADMAN, DAVID J | 1656 | 702-027000 |

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

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❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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| EXAMINER | |
|---|---|
| STEADMAN, DAVID J | |
| ART UNIT | PAPER NUMBER |
| 1656 | |

DATE MAILED: 07/27/2009

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 422 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 422 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.



PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

| Notice of Allowability | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/955,737 | CHOPRA ET AL. | |
| | Examiner | Art Unit | |
| | David J. Steadman | 1656 | |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--***

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the amendment filed on 4/29/09*.

2. ☒ The allowed claim(s) is/are *12-16,18-24,26,27,41 and 44*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE**.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS ( as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review ( PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   **Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 4/19/02
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

## DETAILED ACTION

### *Status of the Application*

**[1]** A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/29/09 has been entered.

**[2]** Applicant's amendment to the claims, filed on 4/29/09, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

### *Information Disclosure Statement*

**[3]** Upon review of the information disclosure statement filed on 4/19/02 and attached to the Office action mailed on 1/26/05, the examiner notes that the publication year for reference 1, Hong et al., is not listed. An updated Form PTO/SB/08 is attached to this Office action, which includes the publication year for the reference of Hong et al.

### *Examiner's Amendment to the Claims*

**[4]** An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Ms. Diana M. Collazo on 7/15/09.

**[5]** The claims have been amended as follows:

Cancel claim 34.

Re-write claim 12 as follows:

Claim 12. A method for identifying a candidate agent that interacts with or binds to a beta-amyloid precursor protein (APP) binding site of Beta-site APP Cleaving Enzyme (BACE), the method comprising:

(a) utilizing the relative three-dimensional structural coordinates of a complex of a BACE peptide and an APP inhibitor peptide according to Figures 1A-1EEE, ± a root mean square deviation from the backbone atoms of the amino acid residues in the complex not more than 1.5Å, to

generate a three-dimensional representation of the complex, wherein:

(i) the BACE peptide in the complex comprises the amino acid sequence of residues 58-447 of SEQ ID NO: 1, and

(ii) the APP inhibitor peptide in the complex comprises the amino acid sequence SEVNStaVAEF (SEQ ID NO:3), wherein Sta is (S)-statine;

(b) identifying the amino acid residues forming the APP binding site of the BACE peptide from the three-dimensional representation in step (a), wherein the APP-binding site comprises the relative structural coordinates according to Figures 1A-1EEE of amino acid residues LYS70, SER71, GLY72, GLN73, GLY74, TYR75, LEU91, VAL92,

ASP93, THR94, GLY95, SER96, SER97, ASN98, TYR129, VAL130, PRO131, TYR132, THR133, GLN134, GLY135, LYS136, TRP137, LYS168, PHE169, PHE170, ILE171, ASN172, SER174, TRP176, GLY178, ILE179, LEU180, GLY181, ALA183, TYR184, ALA185, GLU186, ILE187, ALA188, ARG189, PRO190, ASP191, ASP192, ARG256, TRP258, TYR259, TYR283, ASP284, LYS285, SER286, ILE287, VAL288, ASP289, SER290, GLY291, THR292, THR293, ASN294, LEU295, ARG296, GLY325, GLU326, ARG368, VAL370, LYS382, PHE383, ALA384, ILE385, SER386, GLN387, SER388, SER389, THR390, GLY391, THR392, VAL393, GLY395, ALA396, and ILE447, ± a root mean square deviation from the backbone atoms of said amino acid residues of not more than 1.5Å;

(c) generating a three-dimensional model of the APP binding site of BACE;

(d) employing said three-dimensional model from step (c) to identify said candidate agent;

(e) obtaining said candidate agent; and

(f) contacting *in vitro* or *in vivo* said candidate agent with BACE to determine the ability of said candidate agent to interact or bind to BACE, whereby the detection of the ability of said candidate agent to interact or bind to BACE identifies said candidate agent.

Re-write claim 16 as follows:

Claim 16. The method of Claim 12, wherein the contacting of the candidate agent with BACE comprises determining the effect the agent has on BACE aspartic

protease activity.

Re-write claim 20 as follows:

Claim 20. A method for identifying a candidate agent that interacts with or binds to a beta-amyloid precursor protein (APP) binding site of Beta-site APP Cleaving Enzyme (BACE), the method comprising:

(a) utilizing the relative three-dimensional structural coordinates of a complex of a BACE peptide and an APP inhibitor peptide according to Figures 1A-1EEE, ± a root mean square deviation from the backbone atoms of the amino acid residues in the complex not more than 1.5Å, to generate a three-dimensional representation of the complex, wherein the BACE peptide in the complex comprises the amino acid sequence of residues 58-447 of SEQ ID NO: 1, and the APP inhibitor peptide in the complex comprises the amino acid sequence SEVNStaVAEF (SEQ ID NO:3), wherein Sta is (S)-statine;

(b) identifying the amino acid residues forming the APP binding site of the BACE peptide from the three-dimensional representation in step (a), wherein the APP-binding site comprises the relative structural coordinates according to Figures 1A-1EEE of amino acid residues LYS70, SER71, GLY72, GLN73, GLY74, TYR75, LEU91, VAL92, ASP93, THR94, GLY95, SER96, SER97, ASN98, TYR129, VAL130, PRO131, TYR132, THR133, GLN134, GLY135, LYS136, TRP137, LYS168, PHE169, PHE170, ILE171, ASN172, SER174, TRP176, GLY178, ILE179, LEU180, GLY181, ALA183, TYR184, ALA185, GLU186, ILE187, ALA188, ARG189, PRO190, ASP191, ASP192, ARG256,

TRP258, TYR259, TYR283, ASP284, LYS285, SER286, ILE287, VAL288, ASP289, SER290, GLY291, THR292, THR293, ASN294, LEU295, ARG296, GLY325, GLU326, ARG368, VAL370, LYS382, PHE383, ALA384, ILE385, SER386, GLN387, SER388, SER389, THR390, GLY391, THR392, VAL393, GLY395, ALA396, and ILE447, ± a root mean square deviation from the backbone atoms of said amino acid residues of not more than 1.5Å;

(c) generating a three-dimensional model of the APP binding site of BACE;

(d) employing said three-dimensional model from step (c) to identify said candidate agent;

(e) synthesizing said candidate agent; and

(f) contacting *in vitro* or *in vivo* said candidate agent with BACE to determine the ability of said candidate agent to interact or bind to BACE, whereby the detection of the ability of said candidate agent to interact or bind to BACE identifies said candidate agent.

Re-write claim 24 as follows:

Claim 24. The method of Claim 20, wherein the contacting of the candidate agent with BACE comprises determining the effect the agent has on BACE aspartic protease activity.

Re-write claim 41 as follows:

Claim 41. A method for identifying a candidate agent that interacts with or binds to a beta-amyloid precursor protein (APP) binding site of Beta-site APP Cleaving Enzyme (BACE), the method comprising:

(a) forming a co-crystal of a BACE peptide in complex with an APP inhibitor peptide, wherein said co-crystal has space group I222, and unit cell parameters a=86.627 Å, b=130.861 Å, c=130.729 Å, and α=β=γ=90° and subjecting the co-crystal to X-ray diffraction and collecting data sufficient to determine the three-dimensional coordinates of said complex, wherein:

(i) the BACE peptide in the co-crystal comprises the amino acid sequence of residues 58-447 of SEQ ID NO: 1, and

(ii) the APP inhibitor peptide in the co-crystal comprises the amino acid sequence SEVNStaVAEF (SEQ ID NO:3), wherein Sta is (S)-statine;

(b) utilizing the relative three-dimensional structural coordinates of the complex of a BACE peptide and an APP inhibitor peptide according to Figures 1A-1EEE, ± a root mean square deviation from the backbone atoms of the amino acid residues in the complex not more than 1.5Å, to generate a three-dimensional representation of the complex,

(c) identifying the amino acid residues forming the APP binding site of the BACE peptide from the three-dimensional representation in step (a), wherein the APP-binding site comprises the relative structural coordinates according to Figures 1A-1EEE of amino acid residues LYS70, SER71, GLY72, GLN73, GLY74, TYR75, LEU91, VAL92, ASP93, THR94, GLY95, SER96, SER97, ASN98, TYR129, VAL130, PRO131, TYR132,

THR133, GLN134, GLY135, LYS136, TRP137, LYS168, PHE169, PHE170, ILE171, ASN172, SER174, TRP176, GLY178, ILE179, LEU180, GLY181, ALA183, TYR184, ALA185, GLU186, ILE187, ALA188, ARG189, PRO190, ASP191, ASP192, ARG256, TRP258, TYR259, TYR283, ASP284, LYS285, SER286, ILE287, VAL288, ASP289, SER290, GLY291, THR292, THR293, ASN294, LEU295, ARG296, GLY325, GLU326, ARG368, VAL370, LYS382, PHE383, ALA384, ILE385, SER386, GLN387, SER388, SER389, THR390, GLY391, THR392, VAL393, GLY395, ALA396, and ILE447, ± a root mean square deviation from the backbone atoms of said amino acid residues of not more than 1.5Å;

(d) generating a three-dimensional model of the APP binding site of BACE;

(e) employing said three-dimensional model from step (d) to identify said candidate agent;

(f) obtaining said candidate agent; and

(g) contacting *in vitro* or *in vivo* said candidate agent with BACE to determine the ability of said candidate agent to interact or bind to BACE, whereby the detection of the ability of said candidate agent to interact or bind to BACE identifies said candidate agent.

Re-write claim 44 as follow:

Claim 44. A method for identifying a candidate agent that interacts with or binds to a beta-amyloid precursor protein (APP) binding site of Beta-site APP Cleaving Enzyme (BACE), the method comprising:

(a) utilizing the relative three-dimensional structural coordinates of a complex of a BACE peptide and an APP inhibitor peptide according to Figures 1A-1EEE, ± a root mean square deviation from the backbone atoms of the amino acid residues in the complex not more than 1.5Å, to generate a three-dimensional representation of the complex, wherein the BACE peptide in the complex comprises the amino acid sequence of residues 58-447 of SEQ ID NO: 1, and the APP inhibitor peptide in the complex comprises the amino acid sequence SEVNStaVAEF (SEQ ID NO:3), wherein Sta is (S)-statine;

(b) identifying the amino acid residues forming the APP binding site of the BACE peptide from the three-dimensional representation in step (a), wherein the APP-binding site comprises the relative structural coordinates according to Figures 1A-1EEE of amino acid residues LYS70, SER71, GLY72, GLN73, GLY74, TYR75, LEU91, VAL92, ASP93, THR94, GLY95, SER96, SER97, ASN98, TYR129, VAL130, PRO131, TYR132, THR133, GLN134, GLY135, LYS136, TRP137, LYS168, PHE169, PHE170, ILE171, ASN172, SER174, TRP176, GLY178, ILE179, LEU180, GLY181, ALA183, TYR184, ALA185, GLU186, ILE187, ALA188, ARG189, PRO190, ASP191, ASP192, ARG256, TRP258, TYR259, TYR283, ASP284, LYS285, SER286, ILE287, VAL288, ASP289, SER290, GLY291, THR292, THR293, ASN294, LEU295, ARG296, GLY325, GLU326, ARG368, VAL370, LYS382, PHE383, ALA384, ILE385, SER386, GLN387, SER388, SER389, THR390, GLY391, THR392, VAL393, GLY395, ALA396, and ILE447, ± a root mean square deviation from the backbone atoms of said amino acid residues of not more than 1.5Å;

(c) generating a three-dimensional model of the APP binding site of BACE;

(d) employing said three-dimensional model from step (c) to identify said candidate agent;

(e) obtaining said candidate agent; and

(f) contacting said candidate agent with the APP-binding site of the BACE to determine the ability of said candidate agent to interact or bind to BACE, whereby the detection of the ability of said candidate agent to interact or bind to the APP-binding site of the BACE identifies said candidate agent.

***Examiner's Reasons for Allowance***

**[6]** In view of the instant amendment to the claims filed on 4/29/09 and further in view of the examiner's amendment to the claims as set forth above, the rejections as set forth in the Office action mailed on 10/30/08 are withdrawn.

**[7]** The closest prior art of record is the reference of Tang et al. (US Patent 6,545,127; cited in the IDS filed on 10/29/03), which teaches crystallization of human BACE with a BACE inhibitor and a method of using the structural coordinates obtained from X-ray crystallography using the crystal in a method of rational drug design. The claimed invention is distinguished over Tang because the BACE inhibitor of the crystal of Tang is different from SEQ ID NO:3 herein and it follows that the resulting structural coordinates of Tang are different from those of Figures 1A to 1EEE herein. Also, the difference between the prior art and the claimed invention goes beyond the structural coordinates of Figures 1A to 1EEE herein, *e.g.,* the prior art does not teach identifying

the recited amino acids of the BACE APP-binding site as encompassed by the claims and using a 3D model of those amino acids for rational drug design. As such, the methods of claims 12-16, 18-24, 26-27, 41, and 44 are allowable over the prior art of record.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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